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This Research Paper is accompanied by Invited Editorial, see page 147

Comparison of autonomic dysfunction in patients with Parkinson's Disease, progressive supranuclear palsy, and multiple system atrophy

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ABSTRACT

Aim of the study. To assess and compare autonomic nervous system (ANS) dysfunction, especially cardiovascular dysautonomia, in Parkinson's Disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and healthy controls.

Clinical rationale for the study. Assessment of ANS can be useful in differential diagnosis. Dysautonomia affects quality of life and can lead to potentially life-threatening complications. There is very little literature data regarding dysautonomia in PSP in relation to other parkinsonian syndromes. This study expands the knowledge about ANS dysfunction in parkinsonisms, especially PSP.

Material and methods. Patients with PD, MSA and PSP were prospectively recruited to our study. Demographic data and information about clinical and neuropsychological assessment, medication and comorbidities was collected. SCOPA-AUT questionnaire, 5-minute tilt test, and 5-minute heart rate variability (HRV) analysis in time and frequency domains were used to assess ANS. Analysis was also performed in patients with PSP-RS and PSP-P phenotypes, and in a subgroup with eliminated confounding factors, including age and disease duration.

Results. 76 PD, 25 PSP, and 12 MSA patients, and 20 controls, were included. Symptoms of dysautonomia revealed by a SCOPA-AUT questionnaire were present in all groups of patients. Urinary dysfunction was more pronounced in atypical parkinsonisms, and cardiovascular symptoms in α-synucleinopathies. HRV was disrupted in all groups of patients. However, when PSP-P and PSP-RS phenotypes were considered, HRV was diminished in PSP-RS, but there were no differences in HRV parameters between PSP-P and controls. Neurogenic orthostatic hypotension was present in 25% of PD and 58% of MSA patients, but it was absent in PSP patients and the control group. 13 PD and nine PSP patients and 16 controls were included in subanalysis. This revealed that PSP, but not PD, patients had significantly more symptoms of dysautonomia and lower HRV indices compared to controls, and that orthostatic hypotension was even more common in PD than in controls.

Conclusions and clinical implications. Our study suggests that dysautonomia is common in PD, MSA and PSP, even though it has different profiles in the different diseases. NOH is present in PD and MSA, but not in PSP.

Keywords: Parkinson's Disease, progressive supranuclear palsy, multiple system atrophy, autonomic dysfunction, autonomic nervous system, orthostatic hypotension, heart rate variability, SCOPA-AUT

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Introduction

Autonomic nervous system (ANS) dysfunction is common in α-synucleinopathies. ANS dysfunction includes gastrointestinal disorders, genitourinary dysfunction, problems with thermoregulation, orthostatic hypotension (OH), supine hypertension, and reduced heart rate variability (HRV) [1–3]. In Parkinson's Disease (PD), the prevalence of different symptoms of autonomic dysfunction varies between 14% and 90% depending on the stage of the disease [3]. Some data has even suggested an association between cardiovascular dysautonomia and cognitive decline in PD [1, 2]. In multiple system atrophy (MSA), dysautonomia is more prominent than in PD. OH and genitourinary dysfunction are pivotal symptoms in the diagnostic criteria for MSA [3–5]. The presence of autonomic dysfunction has also been noted in tauopathies such as progressive supranuclear palsy (PSP) [6–10]. However, predominant, and otherwise unexplained, autonomic dysfunction is one of the mandatory exclusion criteria for PSP according to the Movement Disorders Society (MDS) [11]. Cardiovascular autonomic dysfunction, including OH, has been noted in PSP, but it is usually less frequent than in MSA or PD [6–10]. Some studies have not found OH in PSP patients [10, 12]. Several studies have assessed HRV in PD and in MSA, and some of them have even suggested that HRV could be potentially helpful in differential diagnosis between these two diseases [13–15]. However, there is a paucity of data about HRV in PSP, and only a few studies have evaluated HRV in PSP with methods other than assessment of RR interval variation during metronomic deep breathing (RRIV). None of these studies has used HRV analysis with time and frequency domain methods for standard 5 minute short-term recordings [16–18].

Differential diagnosis of parkinsonian syndromes is challenging, especially as PD, PSP-P and MSA-P have overlapping symptoms [12, 19, 20]. In studies with histopathological confirmation, antemortem diagnoses of PSP and MSA were confirmed in 57–70% and 77–83% of patients, respectively [12, 20].

Cost effective, easily accessible methods useful in differential diagnosis of these diseases are required. The evaluation of ANS function, including HRV analysis and the assessment of orthostatic hypotension, could potentially be beneficial [5, 11–15, 19].

Clinical rationale for the study

The aim of this study was the assessment and comparison of ANS dysfunction, especially cardiovascular dysautonomia, in PD, MSA, and PSP patients and in healthy controls using a SCOPA-AUT questionnaire, a tilt test, and short-term HRV analysis in time and frequency domains. We believe that the assessment of dysautonomia is important because it could be useful in differential diagnosis, and because dysautonomia affects quality of life and can lead to potentially life-threatening complications. Literature data regarding dysautonomia in PSP in relation to other parkinsonian syndromes is scarce. Our study expands the knowledge about ANS dysfunction in these diseases, especially PSP.

Material and methods

Patients with a parkinsonian syndrome referred to the Department of Neurology of the Central Clinical Hospital of the Medical University of Silesia in Katowice, Poland between January 2021 and March 2023 were qualified for participation in this study. Inclusion criteria were: a diagnosis of PD, MSA or PSP [4, 5, 11, 21]; capacity to give informed consent to participate in the study; and the physical ability to take part in ANS assessment tests. Patients with diagnoses other than PD, PSP or MSA were excluded. Further exclusion criteria were introduced to minimise the effects of factors possibly related to autonomic dysfunction or affecting its assessment. So, a glomerular filtration rate of below 60 mL/min/1.73 m^2 calculated using the MDRD formula, and present or suspected liver cirrhosis, were exclusion criteria. We thereby reduced the possibility of the presence of a previously undiagnosed polyneuropathy related to chronic kidney disease or liver dysfunction. Patients with diabetes mellitus (DM) were excluded if they had clinically known neurological complications of DM, had HbA1c > 6.5%, were on insulin therapy, or had been diagnosed 5+ years earlier. This was to minimise any effects related to (even subclinical) diabetic neuropathy [22, 23]. Respiratory system diseases affecting breathing rhythm was an exclusion criterion, due to a possible relation between respiratory rate and HRV. Heart diseases are related to OH and reduced HRV, which are correlated with the severity of heart failure. Because of this, patients with New York Heart Association Functional Classification > 1 were also excluded. Non-sinus heart rhythm, heart block and arrhythmia were also exclusion criteria, because their presence could make HRV analysis unreliable. Moderate or severe dementia patients were excluded due to potential problems regarding the reliability of SCOPA-AUT questionnaire data and obtaining informed consent from this subgroup of patients. Diagnoses of peripheral neuropathy, significant electrolyte disturbances, or uncompensated thyroid dysfunction were also exclusion criteria, due to their potential relation to ANS abnormalities.

Diagnoses of PD and PSP were based on the current MDS criteria [11, 21]. MSA diagnosis was made initially according to the criteria from 2008, although during the recruitment period new diagnostic criteria for MSA were published, and we applied these retrospectively to patients we had assessed earlier [4, 5]. Patients with the diagnosis of probable or possible PSP, as well as probable/clinically established and clinically probable/possible MSA were included. The control group was recruited from patients' spouses and caregivers, who did not have any movement disorder or any of the discussed exclusion criteria.

Demographic and clinical data of patients was collected via laboratory tests to confirm eligibility, comorbidities, prescribed medications, and the results of standard neuropsychological and clinical assessments. Information about the presence of depression and dementia was noted. None of the recruited patients were being treated with nitrates, central sympatholytic agents, first generation antipsychotics, or antiarrhythmics other than small doses of β-blockers. Information was also collected about the use of α-adrenergic antagonists, β-blockers, anticholinergics, amantadine, rasagiline and selegiline, renin–angiotensin system antagonists (RAS), dihydropyridine calcium channel blockers, antidepressive drugs, and atypical antipsychotics.

There are scales dedicated to the assessment of MSA and PSP [24, 25], but they have not been translated into and validated in Polish, making it difficult to compare the diseases' severities, so we decided to use the Hoehn-Yahr scale (HYS) and the Polish version of the MDS-Unified Parkinson's Disease Rating Scale part 3 (MDS-UPDRS-3) performed in OFF state, without dopamine replacement therapy (DRT) and performed in ON state after administration of levodopa [26]. Daily levodopa equivalent dose (LEDD) was calculated for all patients [27].

Analysis of all assessed parameters was also performed in the subgroups of PD, PSP and control group participants without any potentially confounding factors such as medications and comorbidities other than arterial hypertension. MSA patients were not included in this subanalysis, due to the limited number of patients without any potentially confounding factor in the MSA group. Due to the fact that differential diagnosis of PSP-P, MSA and PD is especially challenging, additional comparison of autonomic dysfunction profiles for PSP-RS and PSP-P, PD, MSA and control groups was also performed. PSP phenotypes were classified according to MDS criteria. This showed 12 PSP-RS, nine PSP-P, three PSP-PGF, and one PSP-OM [11].

The Polish version of the SCOPA-AUT questionnaire was used to assess subjective complaints of dysautonomia [28]. ANS assessment was performed between 7am and midday with a room temperature of 20-25°C. During autonomic tests, patients had been without DRT for 12+ hours so as to eliminate its potential influence on ANS. However, some effects of long-acting dopamine agonists could not be completely excluded. Patients were also instructed to avoid beverages, alcohol and nicotine on the day of assessment. After 10 minutes of supine rest, 5-minute ECG from lead II was recorded with a Biopac MP150 Acquisition System and related AcqKnowledge software with a sampling rate of 1,000 Hz. A band pass filter of 0.5–35 Hz was applied. Next, ARTiiFACT software was used to correct artifacts and ectopic beats, as well as HRV analysis in time and frequency domains [29]. Artifacts and ectopic beats were detected by visual inspection of the data with the assistance of software algorithms and corrected with cubic spline interpolation. For the time domain, the standard deviation of all normal RR intervals (SDNN) and root mean square of the successive differences between adjacent normal RR intervals (RMSSD) were used. Fast Fourier transform (FFT) algorithm was used for spectral analysis of HRV. High frequency (HF) — 0.15–0.4 Hz, low frequency (LF) — 0.04–0.15 Hz, and very low frequency (VLF) — < 0.04 Hz components were calculated and presented in absolute values. LF and HF components were also presented in normalised units (n.u) and LF/HF ratio was calculated. HRV analysis was performed according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [30]. After 15 minutes of supine rest, head-up tilt test to a 60° angle was performed, and that position was maintained for 5 minutes. Orthostatic hypotension was diagnosed in cases of a sustained systolic blood pressure (SBP) drop ≥ 20 mmHg and/or diastolic blood pressure (DBP) ≥ 10 mmHg within 5 minutes of the tilt test [31]. Changes in SBP (ΔSBP), DBP (ΔDBP) and heart rate (ΔHR) were also analysed in the study. Neurogenic orthostatic hypotension (NOH) was diagnosed in the patients with ΔHR/ΔSBP ratio < 0.5 bpm/mmHg as proposed by Norcliffe-Kaufmann et al. [32].

Statistical analysis was performed using STATISTICA v.13 PL software (Tibico Software Inc.). The quantitative variables were presented as an arithmetic mean and a standard deviation (normally distributed variables) or a median and the interquartile range (variables of non-normal distribution). The normality of distribution and homogeneity of variance assumptions were assessed with the Shapiro–Wilk test and Brown–Forsythe test, respectively. One way ANOVA, Welch's ANOVA, Kruskal-Wallis ANOVA, t-Student test and U-Mann-Whitney test were used in data analysis for quantitative variables. Tukey, Tukey-Kramer and post-hoc test for the Kruskal-Wallis ANOVA provided by Tibico software [33] were applied in post-hoc analysis. Qualitative variables were presented as percentages. To compare qualitative variables, a chi-square test was used. A Fisher's exact or a Chi-square test with Bonferroni correction for multiple comparisons was used for post-hoc comparisons. The cut-off point for p-values was set at 0.05, or, in cases where Bonferroni correction was used, 0.017 or 0.008 or 0.006.

The study protocol was reviewed and approved by the Bioethical Committee of the Medical University of Silesia in Katowice (PCN/0222/KB1/27/I/20) and performed in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all subjects.

Results

There were 201 patients referred to the Department of Neurology of the Central Clinical Hospital of the Medical University of Silesia in Katowice, Poland due to parkinsonian syndrome between January 2021 and March 2023. 88 patients did not meet our already detailed inclusion/exclusion criteria.

Eventually, 113 patients (76 PD, 12 MSA, and 25 PSP) and 20 controls were included in our study. PSP patients were older than PD patients (p = 0.036) and there were significantly more male subjects in PD *vs.* MSA (p = 0.003). Compared to atypical parkinsonian patients, the PD group had a longer disease duration (MSA p = 0.005, PSP p = 0.002) and lower severity on the HYS in the OFF state (MSA p < 0.001, PSP p = 0.026), and on the MDS-UPDRS-3 in the ON state (MSA p < 0.001, PSP p < 0.001). LEDD was significantly higher in PD than PSP (p < 0.002).

There were no significant differences between the assessed groups in terms of the prevalence of depression and dementia. However, the presence of depression and cognitive functions were not assessed in the control group. Arterial hypertension was significantly more common in PSP than PD (p = 0.006). There were no statistically significant differences between the groups in terms of the prevalence of diabetes mellitus, heart diseases or current or history of cancer. β-blockers were more commonly used in MSA patients than in PD patients (p = 0.007). There were significant differences between groups in the numbers of patients using cholinesterase inhibitors, MAO-B inhibitors and atypical antipsychotics, but after Bonferroni correction none of them reached statistical significance in post hoc comparisons. Patients and controls demographics and clinical characteristics, as well as their comparisons, are set out in Table 1.

Assessment with the SCOPA-AUT questionnaire did not reveal any significant differences between patients with PD, PSP and MSA in summary score, total score without sexual domain, or gastrointestinal domain. However, parkinsonian patients regardless of diagnosis had significantly higher results than the control group in their SCOPA-AUT total score (PD p = 0.006, MSA p < 0.001, PSP p = 0.001), SCOPA-AUT total score without sexual domain (PD p = 0.004, MSA p < 0.001, PSP < 0.001), and in gastrointestinal domain (PD p = 0.001, MSA p = 0.016, PSP p < 0.001). In urinary domain, PSP and MSA patients had more points than controls (MSA p < 0.001, PSP p = 0.012). MSA patients had significantly more severe

Table 1. Demographic and clinical characteristic of patients

	PD	MSA	PSP	CG	P-value	Post hoc comparisons
Age (years)	61.7 ± 9.1	68.2 ± 6.3	67.7 ± 5.1	62.5 ± 6.6	< 0.001*	PSP > PD
Sex (% male)	61.8%	16.7%	44%	40%	0.014*	PD > MSA
Disease duration	7 (3–10)	2.5 (2–3.5)	2 (2–5)	–	< 0.001*	PD > MSA, PD > PSP
HYS	2 (2–3)	4 (3–4)	3 (3–4)	–	< 0.001*	PSP > PD, MSA > PD
MDS–UPDRS–3 ON	18 (9–25.5)	38.5 (28.5–61)	46 (31–56)	–	< 0.001*	PSP > PD, MSA > PD
MDS–UPDRS–3 OFF	40.1 ± 19.4	48.2 ± 21.9	45.6 ± 17.7	–	0.251	
LEDD (mg)	810 (420–1,500)	590 (100–980)	300 (0–780)	–	< 0.001*	PD > PSP
Depression	31.6%	58.3%	36%	–	0.197	
Dementia	14.5%	0%	12%	–	0.367	
Diabetes mellitus	3.9%	0%	12%	5%	0.330	
Hypertension	32.9%	66.7%	64%	35%	0.012*	PSP > PD
Heart disease	8.6%	33.3%	8%	10%	0.061	
Cancer	5.3%	0	0	15%	0.119	
Medications:						
α–adrenergic antagonists	9.2%	8.3%	16.0%	0%	0.324	
β–blockers	13.2%	50.0%	28.0%	20%	0.020*	MSA > PD
Anticholinergics	9.2%	8.3%	4.0%	0%	0.472	
Amantadine	17.1%	8.3%	8.0%	0%	0.163	
Selegiline/Rasagiline	22.4%	8.3%	4.0%	0%	0.019*	
Cholinesterase inhibitors	6.6%	0%	20.0%	0%	0.010*	
RAS	18.4%	25.0%	36.0%	5%	0.071	
Diuretics	10.5%	16.7%	20%	0%	0.184	
SSRI	15.8	50.0%	24.0%	0%	0.004*	MSA > CG
Other anti-depressants	5.3%	0%	4.0%	0%	0.631	
Atypical antipsychotics	14.5%	0%	0%	0%	0.029*	
Calcium-blockers	7.9%	16.7%	12.0%	10.0%	0.779	

*significant differences; HYS — Hoehn-Yahr scale; MDS-UPDRS-3 — 3rd part of MDS – Unified Parkinson's Disease Rating Scale; LEDD — daily levodopa equivalent dose; RAS — renin-angiotensin system antagonists; SSRI — selective serotonin reuptake inhibitors

urinary dysfunction than PD patients (p = 0.040). In cardiovascular domain, patients with PD and MSA had significantly more severe complaints than did the control group (PD p = 0.025, MSA p = 0.003). There were no significant differences between groups in thermoregulatory domain. No differences between groups in pupillomotor domain were found in post hoc analysis. The numbers of sexually active participants were not equal in groups (p = 0.018), but there were no significant differences in post hoc analysis or in SCOPA-AUT sexual domain score.

HRV analysis revealed that the MSA group had a shorter mean NN interval than the control group (p = 0.020). There were significant differences between all groups of patients and controls in terms of SDNN (PD p < 0.001, MSA p < 0.001, PSP p = 0.002), as well as in the power of VLF (p < 0.001 for all groups) and LF (PD p = 0.007, MSA p = 0.002, PSP p = 0.001) bands. RMSSD was significantly different only for the MSA and control groups (p = 0.002). Power of HF band was lower in MSA and PSP than in the control group (MSA p = 0.004, PSP p = 0.048). Kruskal Wallis test did not reveal significant differences for LF and HF bands presented in n.u. as well as LF/HF bands ratio. Post hoc tests did not reveal any significant differences between PD, MSA and PSP in HRV analysis. However, there was an insignificant tendency to a lower HRV in MSA patients.

PD and MSA patients had a higher SBP drop than controls (PD p = 0.028, MSA p < 0.001). The MSA group had a significantly larger SBP drop than the PSP group (p = 0.002). ΔDBP was significantly larger in MSA than in the control group (p = 0.040). ΔHR was not equal between the groups, but post hoc tests did not reveal statistically significant differences. The number of patients with an SBP drop ≥ 20 mmHg was significantly higher in PD (p = 0.002) and MSA (p < 0.001) than in PSP. More patients in the MSA group had an SBP drop ≥ 20 mmHg than in the control group (p < 0.001). There were differences between groups in the number of patients with a DBP drop ≥ 10 mmHg, but this did not reach the cut-off point in post hoc tests. Both SBP and DBP drops below the cut-off point were more common in the MSA than in the PSP (p = 0.002) and control groups (p = 0.004). There were differences in the presence of NOH between PD and PSP (p = 0.003), between MSA and PSP (p < 0.001), and between MSA and controls (p < 0.001). All the details are set out in Table 2.

In subanalysis of a group of patients with eliminated confounders, PSP patients had more pronounced symptoms of dysautonomia in SCOPA-AUT questionnaire than did controls in total score (p = 0.002), total score without sexual domain (p < 0.001), gastrointestinal domain (p = 0.011), and urinary domain (p < 0.001). SCOPA-AUT total score was significantly higher in PSP compared to PD (p = 0.039). HRV analysis revealed significant differences between PSP and controls in SDNN (p = 0.006), VLF (p = 0.006), LF (p = 0.009) and HF (p = 0.012) band absolute values. NOH was present in four (30.7%) PD patients, and a significantly larger ΔSBP was found in this group than in controls (p = 0.016). ANS assessment and subgroup characteristics are set out in Supplementary Table 2.

Analysis with separate assessment of PSP-P and PSP-RS revealed that gastrointestinal (p < 0.001) and urinary (p = 0.012) domains were significantly more affected in PSP-P, but not in PSP-RS, compared to the control group. PSP-RS had more cardiovascular symptoms declared in SCOPA-AUT (p = 0.020). There were no significant differences in ANS dysfunction measured with SCOPA-AUT between the diseases in this subanalysis. PSP-RS patients had lower SDNN, VLF, LF and HF than controls. HRV was not significantly affected in the PSP-P subgroup compared to controls. PSP-RS, but not PSP-P, patients less commonly declared sexual activity (p = 0.002) than controls. Demographics of PSP-P and PSP-RS and details of this subanalysis are presented in Supplementary Tables 3 and 4.

Discussion

In our study, as in previously published data, symptoms assessed with the SCOPA-AUT questionnaire were present in all of the studied parkinsonian diseases, with some predominance of cardiovascular symptoms in α-synucleinopathies and more severe urinary dysfunction in atypical parkinsonisms, especially MSA [8–10, 12].

A recent systematic review found that symptoms of autonomic dysfunction in PSP are common [10]. In Baschieri et al.'s [10] paper, as in our study, gastrointestinal, urogenital and sudomotor dysfunctions had similar or even greater severity in PSP compared to PD, and were similar or less severe compared to MSA. The only exception was pupillomotor function, which seems to be most affected in PSP. However, some symptoms of dysautonomia in PSP could also be related to other factors such as the advanced age of patients or the destruction of some neural circuits not associated with ANS [10].

Only a few studies have assessed HRV in PSP compared to other parkinsonian syndromes. Most of them assessed RRIV and revealed parasympathetic dysfunction in PSP [6, 9, 12, 34], but some studies did not find any difference between PSP and healthy controls [35, 36]. RRIV was usually similarly affected in PD and PSP and most affected in MSA [9, 34–36]. A very few studies have used spectral or time domain HRV analysis. In one study, that used 15 minute recordings performed during supine rest for spectral analysis of HRV with FFT, the authors did not find differences between MSA and PSP patients, but both groups had lower total power of HRV than controls [18]. In another study assessing PD, PSP and MSA patients, it was found that they had significantly lower LF band relative power of heart rate in all patient groups and decreased LF/HF ratio in MSA and PSP [16]. One study found that a very small group of patients with PSP and CBD had lower absolute power of LF and HF bands and RMSSD than healthy controls in 24-hour ECG during the day and night [17]. In our study, PSP patients had lower HRV than controls, which is in agreement with most

Table 2. ANS assessment in all patients

	PD	MSA	PSP	Control group	p-value
SCOPA–AUT					
Sum	13 (7–18.5)	20 (12–31)	15.5 (9.5–21.5)	5 (3–11)	< 0.001*
		PD, MSA, PSP > control group			
Sum without sexual domain	12 (6–17.5)	20 (11–28)	14 (9–20)	5 (3–9.5)	< 0.001*
		PD, MSA, PSP > control group			
Gastrointestinal domain	3 (1–6)	5,5 (1–6.5)	4.5 (2–7)	1 (0–1)	< 0.001*
		PD, MSA, PSP > control group			
Urinary domain	5 (2–7)	8 (5.5–13.5)	6 (3–8.5)	2.5 (1–4.5)	< 0.001*
		PSP > control group, MSA > control group, MSA > PD			
Cardiovascular domain	1 (0–2)	2 (0.5–6)	0 (0–2)	0 (0–0)	0.001*
		MSA > control group, PD > control group			
Thermoregulatory domain	2 (0–4)	3.5 (0.5–5)	2 (0.5–3.5)	1 (0–2)	0.198
Pupillomotor domain	0 (0–1)	0 (0–0)	1 (0–1.5)	0 (0–1)	0.046*
Sexually active	60.5%	33.3%	36.0%	75%	0.018*
Sexual domain	1 (0–2)	3 (1.5–5)	1 (0–4)	0 (0–1)	0.206†
HRV analysis					
Mean NN [ms]	873.9 ± 131.1	808.8 ± 137.0	923.6 ± 118.7	951.9 ± 103.0	0.010*
		MSA < control group			
SDNN [ms]	22.0 (15.9–33.2)	15.6 (12.2–21.9)	19.7 (14.0–34.5)	36.6 (29.1–44.4)	< 0.001*
		PD, MSA, PSP < control group			
RMSSD [ms]	14.3 (9.4–20.3)	10.1 (6.8–12.0)	14..4 (9.4–28.4)	17.8 (15.1–22.1)	0.005*
		MSA < control group			
VLF [ms2]	194.9 (92.7–377.1)	130.3 (59.3–189.1)	181.7 (92.4–272.9)	609.3 (450.7–957.2)	< 0.001*
		PD, MSA, PSP < control group			
LF [ms2]	92.7 (36.0–197.2)	51.2 (25.7–96.4)	58.5 (31.3–124.1)	231.6 (132.3–365.5)	< 0.001*
		PD, MSA, PSP < control group			
HF [ms2[	60.2 (25.6–140.1)	22.8 (15.6–36.7)	58.5 (31.3–124.1)	104.4 (73.5–193.0)	0.004*
		MSA, PSP < control group			
LF [n.u.]	61.9 (46.6–77.0)	68.8 (50.9–83.3)	63.8 (51.1–71.7)	62.9 (54.0–77.7)	0.847
HF [n.u.]	38.0 (23.0–53.4)	31.2 (16.8–49.1)	36.2 (28.3–48.9)	37.1 (22.3–46.0)	0.847
LF/HF ratio	1.6 (0.9–3.3)	2.3 (1.0–5.0)	1.8 (1.–2.5)	1.6 (1.2–3.5)	0.847
Orthostatic hypotension assessment					
ΔSBP [mmHg]	11.4 ± 14.4	22.2 ± 20.7	1.7 ± 10.2	–0.7 ± 9.7	< 0.001*
		MSA, PD > control group, MSA > PSP			
ΔDBP [mmHg]	1.7 ± 8.2	5.1 ± 10.4	–2.6 ± 6.2	–3.4 ± 6.1	0.004*
		MSA > control group			
ΔHR [bpm]	9.7 ± 6.3	5.4 ± 6.0	7,6 ± 3.9	10.1 ± 4.4	0.041*
SBP drop ≥ 20 mmHg	20 (26.3%)	7 (58.3%)	0 (0%)	0 (0%)	< 0.001*
		PD > PSP, MSA > PSP, control group			
DBP drop ≥ 10 mmHg	17 (22.4%)	5 (41.7%)	1 (4.0%)	1 (5.0%)	0.011*
SBP ≥ 20 mmHg and DBP ≥ 10 mmHg	14 (18.4%)	5 (41.7%)	0 (0%)	0 (0%)	0.001*
		MSA > PSP, MSA > control group			
NOH	19 (25.0%)	7 (58.3%)	0 (0%)	0 (0%)	< 0.001*
		PD > PSP, MSA > PSP, MSA > control group			

*significant differences; † — sexual domain of SCOPA-AUT was not analysed in MSA due to too small a number of sexually active MSA patients; PD — Parkinson's Disease; MSA — multiple system atrophy; PSP — progressive supranuclear palsy; HRV — heart rate variability; SDNN — standard deviation of all normal RR intervals; RMSSD — root mean square of successive differences between adjacent normal RR intervals; VLF — power of very low frequency band; LF — power of low frequency band; HF — power of high frequency band; SBP — systolic blood pressure; DBP — diastolic blood pressure; NOH — neurogenic orthostatic hypotension

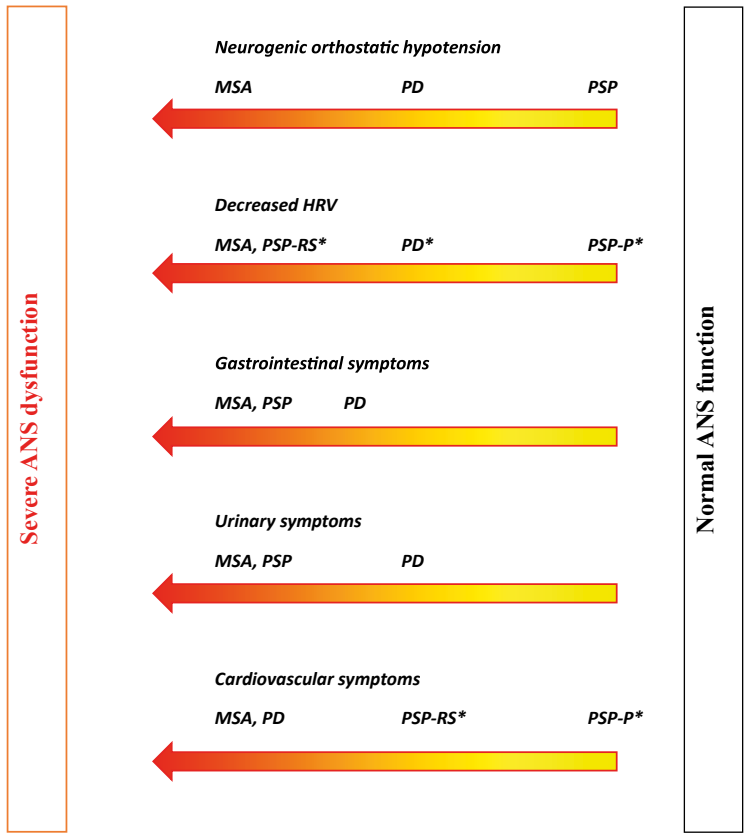

Figure 1. Model of a potential profile of ANS dysfunction based on our results. *based on subanalysis results

[6, 9, 12, 17, 18, 34], but not all [35, 36], of the studies. In those studies which have used time and/or frequency domain HRV analysis, similar results were found by Ochi et al. and Brefel et al. [17, 18]. However, Friedrich et al. found differences between groups and controls in relative LF band power and LF/HF ratio, differences which were absent from our study [16].

The differences between studies might be related to the differing methods of HRV analysis and the use of older diagnostic criteria in some studies. SDNN and LF bands reflect the activity of both parasympathetic and sympathetic ANS, but in short-term resting recordings like those used in our study are predominantly related to parasympathetic ANS [37]. It has also been suggested that the LF band could be mainly related to baroreflex activity [38]. The RMSSD and HF bands reflect parasympathetic activity, and the HF band corresponds with HR variation related to respiration [37, 38]. A physiological explanation of the VLF band is less clear. Some data suggests that it may be intrinsically generated by the heart and modulated by the sympathetic nervous system due to stress or physical activity. It is also associated with thermoregulatory, renin–-angiotensin, and endothelial influences on the heart [37]. The LF/HF ratio is considered a marker of sympatho-vagal balance, however this is controversial because of the large influence of parasympathetic activity on the LF band, especially in resting short-term recordings [37].

Considering all these facts, in our study HRV analysis mainly reflects parasympathetic ANS activity, and suggests that in all of the studied parkinsonian diseases parasympathetic heart regulation is disrupted. The abnormal HRV in PSP-RS and the preserved HRV in PSP-P seen in our study might suggest potential differences in HRV between phenotypes, that have not been previously reported, and should be taken into consideration in future studies.

The prevalence of OH is 0–45% in PSP, 9.6–64.9% in PD with a point prevalence of nearly 30%, and almost 50% in an early stage of MSA to a peak prevalence of 75–81% in European and American cohorts, while it is 5–30% in the general older population [10, 39–41]. In cross-sectional studies, the prevalence of OH in PSP was 0% in four studies, and 8–33% in the remaining five cross-sectional studies [7–10, 34, 35, 42–45]. However, four of the five cross-sectional studies that found OH in PSP were performed in the same cohort of patients [7–10, 34, 42].

In studies where the PSP diagnosis was confirmed by histopathological assessment, the prevalence of OH was 0%, 9% and 45%, in the studies by van Gerpen et al., Oliveira et al., and Wenning et al., respectively [12, 46, 47]. However, in the study by Wenning et al., only one patient with PSP (4%) had OH, which could not be related to drugs, and comorbidities were not specified in that study [47].

In summary, the differences between studies reporting the prevalence of OH in PSP are related to several factors. The studies used different cut-off points for a diagnosis of OH and had different times of assessment, varying from three to 10 minutes. Most of the studies excluded patients with significant comorbidities and/or who were taking drugs affecting the autonomic nervous system. The less strict exclusion criteria used in some studies might also be related to the higher prevalence of OH, possibly associated with comorbidities [7–10, 12, 34, 35, 42–47]. In some studies, dopaminergic treatment during orthostatic test was not specified. Two out of three studies where orthostatic tests were performed after a drugs wash out did not reveal OH in PSP [9, 10, 12, 35]. On the other hand, the effect of dopaminergic drugs on OH might be overestimated [48, 49]. In our study, NOH was present in MSA and PD, but not in PSP and controls, which seems to be in agreement with most previous studies. NOH is related to sympathetic dysfunction, and the absence of NOH in PSP suggests that cardiovascular sympathetic ANS is preserved in PSP but not in MSA and PD, which is in agreement with some previous data [9, 10, 12]. We excluded patients with comorbidities strongly affecting ANS and performed a tilt test after DRT washout, which might have contributed to a lower prevalence of OH compared to some of the studies assessing OH in PSP and a general population [10, 39]. Our results are in agreement with studies which assessed patients after DRT washout [9, 10, 12, 35]. In all PSP patients, as well as in a general geriatric population, the prevalence of OH related to factors other than disease might be 20%, and may still contribute to complications such as falls [50].

We are aware of some limitations of our study. The first major limitation is a lack of histopathological confirmation of the diagnosis in the enrolled patients. Secondly, we were unable to rule out the presence of confounders which could potentially affect ANS assessment. Next, the relatively small number of enrolled patients was a limitation, especially for the subanalysis. However, MSA and PSP are rare diseases. Most elderly patients, including parkinsonian patients, have several comorbidities and take medications affecting the results of ANS tests. Even with the quite liberal patient recruitment criteria in our study, plenty of patients must have been excluded. This problem was partially resolved for PD and PSP by subanalysis of age-matched smaller groups without confounders. We also used a criterion devised by Norcliffe-Kaufmann et al. [32] to differentiate NOH from OH related to drugs and some comorbidities, and this showed that most of the patients in our study had NOH.

Clinical implications/future directions

Our study suggests that dysautonomia is common in PD, MSA and PSP, despite having different profiles in the diseases. Despite some controversies, dysautonomia is present in PSP and should also be assessed in this group of patients, due to its relevant consequences. NOH is present in PD and MSA, but not in PSP. The presence of NOH suggests a diagnosis other than PSP, and this is in agreement with the current criteria and should prove useful in differential diagnosis [5, 11].

There is a possibility that analysis of a larger group of patients might make HRV analysis a useful tool in differential diagnosis of these diseases, but its interference with comorbidities and drugs make this feasible only in some patients. A larger study is needed to establish the presence and clinical significance of dysautonomia in PSP, especially HRV abnormalities and its potential differences in various phenotypes of the disease.

Article information

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